The Incidence and Gastrointestinal Infectious Risk of Functional Gastrointestinal Disorders in a Healthy US Adult Population

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OBJECTIVES: **Functional gastrointestinal disorders (FGDs) are recognized sequelae of infectious gastroenteritis (IGE). Within the active duty military population, a group with known high IGE rates, the population-based incidence, risk factors, and attributable burden of care referable to FGD after IGE are poorly defined.**

METHODS: **Using electronic medical encounter data (1999–2007) on active duty US military, a matched, case-control study describing the epidemiology and risk determinants of FGD (irritable bowel syndrome (IBS), functional constipation (FC), functional diarrhea (FD), dyspepsia (D)) was conducted. Incidence rates and duration of FGD-related medical care were estimated, and conditional logistic regression was utilized to evaluate FGD risk after IGE.**

RESULTS: **A total of 31,866 cases of FGD identified were distributed as follows: FC 55% (n=17,538), D 21.2% (n=6,750), FD 2.1% (n=674), IBS 28.5% (n=9,091). Previous IGE episodes were distributed as follows: specific bacterial pathogen (n=65, 1.2%), bacterial, with no pathogen specified (n=2155, 38.9%), protozoal (n=38, 0.7%), viral (n=3431, 61.9%). A significant association between IGE and all FGD (odds ratio (OR) 2.64; P<0.001) was seen, with highest risk for FD (OR 6.28, P<0.001) and IBS (OR 3.72, P<0.001), and moderate risk for FC (2.15, P<0.001) and D (OR 2.39, P<0.001). Risk generally increased with temporal proximity to, and bacterial etiology of, exposure. Duration of FGD-related care was prolonged with 22.7% having FGD-associated medical encounters 5 years after diagnosis.**

CONCLUSIONS: **FGD are common in this population at high risk for IGE. When considering effective countermeasures and mitigation strategies, attention directed toward prevention as well as the acute and chronic sequelae of these infections is needed.**

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INTRODUCTION

Functional gastrointestinal disorders (FGDs) is a term used to define several variable combinations of chronic or recurrent gastrointestinal (GI) symptoms with no identified underlying pathoetiology (1). In the absence of any diagnostic test or biomarker, the identification and classification of FGDs are symptom based, most often using the widely accepted classification based on the 'Rome diagnostic criteria,' which classify 24 FGDs into esophageal, gastroduodenal, bowel, biliary, anorectal, and abdominal pain subcategories. As a group of conditions, functional disorders were estimated to account for more than 11 million ambulatory care visits in 2004, roughly equating to four visits per every 100 persons in the United States (2), making them one of the most costly and burdensome group of gastrointestinal disorders with considerable societal impact. Although the pathoetiology of these disorders is poorly understood and likely multifactorial, several general mechanisms including gut–brain axis dysfunction, mucosal barrier disruption, gastrointestinal dysmotility, microbiota disturbances, inflammation, visceral hypersensitivity, diet, and genetic predisposition have been implicated in the generation of symptoms associated with these disorders (3,4).

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Most cases of FGD are not linked to any specific instigating event, though an accumulation of evidence linking one FGD in particular, irritable bowel syndrome (IBS), to an antecedent episode of infectious gastroenteritis (IGE), has been amassed and described in two recent meta-analyses demonstrating that IBS risk increases six- to sevenfold after a gastrointestinal infection (5,6), and remains elevated for at least 2 to 3 years after the initial infection (6). Although not as well evidenced, other studies have identified a potential link between IGE and other functional disorders including dyspepsia (D) (7), functional diarrhea (FD) (8), and functional constipation (FC) in returning travelers to high-risk regions (9,10). Although most studies have looked at all-cause, clinic visit, or self-reported IGE exposure, a limited number of studies have emerged linking specific infections such as Campylobacter, Shigella, and Salmonella with IBS (7,11,12), as well as *Salmonella* and *Giardia* with functional D (7,13).

Previous studies using the Defense Medical Surveillance System have identified a higher risk of inflammatory bowel disease (14), Guillain-Barré syndrome (15), and reactive arthritis (16) with antecedent episodes of IGE among active duty military beneficiaries. The purpose of this study is to describe the epidemiology of FGDs among this same population, as well as to evaluate the risk of select functional gastrointestinal sequelae after an antecedent episode of IGE in a generally healthy population with unrestricted health care access.

METHODS

Database information

Data were obtained from the Defense Medical Surveillance System, the main repository for medical data of Department of Defense (DoD) beneficiaries maintained by the Armed Forces Health Surveillance Center (17,18). All subjects were active duty US military personnel who served between 1999 and 2007. Medical information was derived from ambulatory and inpatient claims data for care provided within the Military Health System. Demographic data were derived from personnel information; deployment data were derived from deployment rosters and deployment health assessments. Included data were linked at the individual level and compiled into a single de-identified dataset, which was then provided to the study investigators. The study was reviewed and approved by the Naval Medical Research Center Institutional Review Board in compliance with all applicable regulations governing the protection of human subjects.

FGD case identification and control selection

The primary outcomes were select FGDs including FC, D, FD, and IBS. A case was identified when she/he had at least two International Classification Of Disease, ninth revision, Clinical Modification (ICD9-CM) specific medical encounters for a given FGD diagnosis within 1 year. The FGD ICD9-CM codes utilized for this study were as follows: FC (564.0; all subgroups), non-ulcer D (536.8), FD (564.5), and IBS (564.1). Subsequent medical encounters were determined to be related to the FGD if the ICD9-CM code which classified a subject as a case was included in any of the diagnostic positions.

Each case was matched by time (a medical encounter within 1 calendar year), sex, and age (within 1 year) with up to four subjects with an unrelated diagnosis (controls). These controls were randomly selected from the same population that produced the cases (i.e., active duty military personnel) with a myriad of medical encounter visit types such as vaccinations, procedures, or other unrelated diagnoses. Incident FGD onset was defined as the first documented ambulatory or inpatient medical encounter with an ICD9-CM code listed above.

Exposure

The primary exposure variable of interest was IGE within 24 months before a diagnosis of an incident FGD (cases) or censure (controls). An IGE exposure was defined by ICD9-CM codes for specific pathogens and non-specific infectious enteritis as previously reported (14). Non-specific IGE codes were included because of the lack of routine microbiology performed on patients with IGE in similar healthcare settings (19). Both specific and non-specific codes were utilized to classify an exposure as a specific bacterial, non-specific bacterial, protozoal, or viral etiology. We also evaluated exposures at 24, 18, 12, and 6 months before the FGD diagnosis or censure to assess the temporal relationship between exposure and outcome. Although previous studies have evaluated associations of exposure up to 1 year, we chose to extend exposure windows up until 24 months (6) to account for potential in diagnostic delay because of patient's care seeking behavior and/or provider diagnosis. Owing to the similarities in clinical presentation between the exposures and symptoms of the FGD outcomes of interest, we evaluated a 6-month diagnostic delay window, whereby exposures occurring within 6 months before FGD diagnosis (or censoring for controls) were excluded (14). In addition to IGE exposure, other demographic variables available in the data were evaluated, including: race, military rank, educational attainment, marital status, and branch of service. In addition, on a limited subset of data psychological co-diagnoses were available for initial FGID visit and censure visit for controls. The following ICD-9 codes were used for the axis I disorders: 295—schizophrenic disorders, 296—affective psychoses, 297—paranoid states, 298—other non-organic psychoses. Axis II disorders were defined by the following ICD-9 codes: 300—neurotic disorders, 301—personality disorders, 302—sexual disorders, 308—acute reaction to stress, 309—adjustment reaction, 310—non-psychotic brain syndrome, 311—depressive disorder not elsewhere classified, 312—conduct disturbance not elsewhere classified, 313—emotional disturbance child/adolescent, 314—yperkinetic syndrome.

Analysis

FGD incidence was estimated using the number of incident cases in a given year and the total number of active duty service members for that same year. The associations between each of the FGD, IGE, and covariates were initially explored by univariate methods. All analyses evaluated each FGD independently. Univariate and

multivariate conditional logistic regression models were used to evaluate the relationship between IGE, other covariates, and FGD. For the multivariate models, a backwards elimination approach was used, whereby all variables were initially added to the models. The variable with the largest insignificant *P*-value was removed, and the models were refit. This process was continued iteratively until all variables retained in the models were significant at the $\alpha = 0.15$ level (20). Effect modification was assessed statistically utilizing a multiplicative approach. The association of psychological comorbidity among cases and controls was also evaluated, but limited to concomitant diagnosis for initial FGD visit of incident diagnosis and at censure visit for controls.

Statistical analyses were performed using SAS vs. 8.2 for Windows (SAS Institute, Cary, NC). Two-tailed statistical significance was evaluated using an α of 0.05.

RESULTS

As shown in **Table 1**, a total of 31,866 cases of incident FGD were identified in active duty US military personnel between

Table 1. Demographic characteristics of US military service members diagnosed with FGDs between 1999 and 2007 and their matched controls

Variable	Constipation (*n*=17,538)	Dyspepsia (*n*=6,750)	Functional diarrhea (*n*=674)	IBS (*n*=9,091)	All FGD (*n*=31,866)	Controls[a] (*n*=126,909)
Mean (standard deviation) age	27.27 (8.11)	31.36 (8.79)	30.47 (7.91)	29.82 (7.94)	28.77 (8.40)	28.75 (8.39)
Male Gender[b]	7,898 (45.03)	4,701 (69.64)	523 (77.60)	5,181 (56.99)	17,362 (54.48)	69,432 (54.71)
Race/ethnicity						
White	8,952 (51.04)	4,020 (59.56)	484 (71.81)	6,195 (68.14)	18,385 (57.69)	76,377 (60.18)
Black	5,599 (31.92)	1,475 (21.85)	94 (13.95)	1,561 (17.17)	8,125 (25.50)	25,939 (20.44)
Other	2,987 (17.03)	1,255 (18.59)	96 (14.24)	1,335 (14.68)	5,356 (16.81)	24,593 (19.38)
Marital status[c]						
Married	7,715 (43.99)	4,070 (60.30)	428 (63.50)	5,188 (57.07)	16,244 (50.98)	61,135 (48.17)
Single	8,813 (50.25)	2,293 (33.97)	202 (29.97)	3,314 (36.45)	13,767 (43.20)	59,651 (47.00)
Other	963 (5.49)	376 (5.57)	43 (6.38)	567 (6.24)	1,781 (5.59)	5,868 (4.62)
Unknown	47 (0.27)	11 (0.16)	1 (0.15)	22 (0.24)	74 (0.23)	255 (0.20)
Branch of service						
Army	7,228 (41.21)	2,386 (35.35)	284 (42.14)	3,075 (33.82)	12,168 (38.18)	48,828 (38.47)
Air Force	4,645 (26.49)	2,273 (33.67)	216 (32.05)	3,261 (35.87)	9,614 (30.17)	32,917 (25.94)
Marines	1,589 (9.06)	477 (7.07)	35 (5.19)	614 (6.75)	2,598 (8.15)	12,629 (9.95)
Navy	4,076 (23.24)	1,614 (23.91)	130 (20.62)	2,141 (23.55)	7,486 (23.49)	32,535 (25.64)
Enlisted rank	15,841 (90.32)	5,572 (82.55)	561 (83.23)	7,560 (83.16)	27,678 (86.86)	105,860 (83.41)
Education						
<Bachelor's	14,822 (84.51)	5,228 (77.45)	537 (79.67)	7,127 (78.40)	25,972 (81.50)	98,818 (77.87)
≥Bachelor's	2,169 (12.37)	1,360 (20.15)	123 (18.25)	1,750 (19.25)	5,016 (15.74)	23,773 (18.73)
Unknown	547 (3.12)	162 (2.40)	14 (2.08)	214 (2.35)	878 (2.76)	4,318 (3.40)
Prior infectious diarrhea dx						
6 Months pre-censure	492 (2.81)	179 (2.65)	54 (8.01)	463 (5.09)	1,097 (3.44)	1,248 (0.98)
12 Months pre-censure	740 (4.22)	252 (3.73)	73 (10.83)	678 (7.46)	1,592 (5.00)	2,170 (1.71)
18 Months pre-censure	905 (5.16)	312 (4.62)	82 (12.17)	787 (8.66)	1,911 (6.00)	2,805 (2.21)
24 Months pre-censure	1,024 (5.84)	365 (5.41)	93 (13.8)	887 (9.76)	2,175 (6.83)	3,367 (2.65)
Axis I concomitant diagnoses	43 (0.25)	16 (0.24)	1 (0.15)	26 (0.29)	84 (0.26)	729 (0.57)
Axis II concomitant diagnoses	297 (1.69)	139 (2.06)	7 (1.04)	330 (3.63)	727 (2.28)	3,638 (2.87)

dx, diagnosis; IBS, irritable bowel syndrome; FGD, functional gastrointestinal disorder.
[a]Matched on time of diagnosis (same calendar year), sex, and age.
[b]Eight observations missing.
[c]The control group shown is the complete control group for all matched FGD cases.

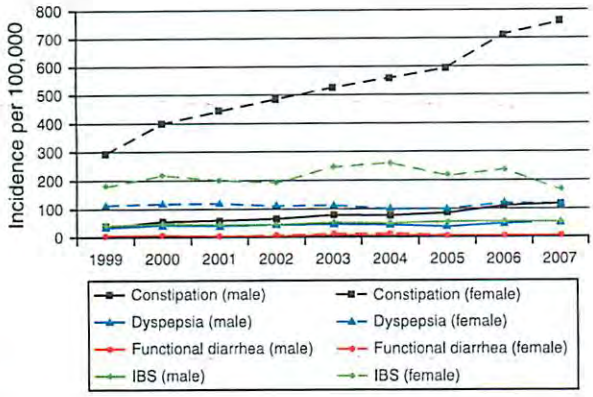

Figure 1. Incidence of functional gastrointestinal disorders by gender. IBS, irritable bowel syndrome.

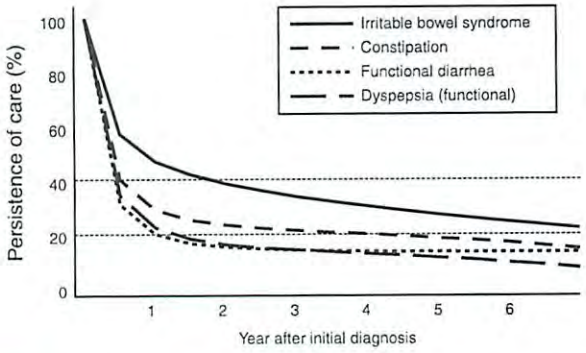

Figure 2. Prevalence of functional gastrointestinal disorder-associated medical visits after initial diagnosis among US military service members remaining on active duty.

1999 and 2007 with the following distribution: FC ($n=17,538$), D ($n=6,750$), FD ($n=674$), and IBS ($n=9,091$). Just over 2,000 cases meet the case definition for more than 1 of the FGD outcomes and were included in each analysis. The most common pattern of FGD overlap was IBS and FC ($n=1209$), followed by IBS and D ($n=477$), and FC and D ($n=385$). The incidence of each of these FGD over the 9-year period is shown in **Figure 1** by gender. Overall incidence of any FGD was 231 per 100,000 person-years (p-yrs; 95% confidence interval (CI): 229, 234), with females having a higher incidence (721 per 100,000 p-yrs) compared with males (147 per 100,000 p-yrs; $P<0.001$). Overall incidence for IBS was estimated at 66 (95% CI: 65, 67) per 100,000 p-yrs (female 195 and male 44 per 100,000 p-yrs, respectively; $P<0.001$). Additionally, although the incidence of IBS demonstrated a peaked curve among females (cresting at 2004), it remained relatively constant among males. The incidence of D remained relatively constant for both males and females over time (102 and 40 per 100,000 p-yrs for females and males, respectively), and FC appeared to increase consistently over the evaluated period for both genders, with a higher rate of increase for females. FC was the most frequent FGD identified in this study (127 per 100,000 p-yrs), with rates seven-fold higher in females compared with males (480 per 100,000 p-yrs vs. 67 per 100,000 p-yrs; $P<0.001$). The incidence of FD fluctuated from 4 to 18/100,000 p-yrs (average incidence 5 per 100,000 p-yrs) with a peak incidence in 2004 and the lowest incidence the following year.

The majority of cases and controls were Caucasian, married, and had no education beyond high school. There were some differences in the demographic profile of cases in the four FGD evaluated. Specifically, cases with FC were more commonly of female gender ($P<0.001$) and single ($P<0.001$). The three major branches of the US Military Armed Forces (Army, Navy, and Air Force) comprised the majority of the study population, with most classified as enlisted personnel. Etiological category of previous IGE episodes were distributed as follows: specific bacterial pathogens ($n=65$, 1.2%), non-specific bacterial ($n=2155$, 38.9%), protozoal ($n=38$, 0.7%), and viral ($n=3431$, 61.9%).

As shown in **Figure 2**, although the majority (65.6%) of cases stopped reporting for care of their FGD within 1 year after initial diagnosis, some (18.4%) continued to seek medical treatment for up to 7 years and there was a longer duration of care seeking for IBS compared with the other FGDs (all $P<0.001$).

Initial univariate analyses (**Table 2**) found that the following covariates were independently associated with at least one of the incident FGD: self-classification as married, having a high school education or less, not being of Caucasian race, and a previous IGE episode. Interestingly, being of a race other than Caucasian has a significantly higher likelihood of FC and D and was less likely to have FD and IBS.

The odds ratio (OR) for incident FGD after an antecedent episode of IGE increased as the timeframe allotted for exposure decreased. When limiting the IGE episodes to only those of bacterial origin (specific and non-specific) in 24 months before the censure, the associated OR increased for D (9%), FD (41%), and IBS (13%), and remained essentially unchanged for FC. A similar inverse relationship was observed between the OR and timeframe from exposure to censure when stratifying by viral and bacterial etiologies (**Table 2**).

In the multivariate models, after controlling for the other covariates, being married, having less than a bachelor's degree, being in the Army or the Air Force, and having an episode of IGE in 24 months before the censure significantly increased the risk of each FGD (**Table 3**). In contrast, being in the Marines appeared to be protective (Navy referent). Being classified as non-Caucasian increased the risk of FC and D and subsequently decreased the risk of FD and IBS. The relative risk estimates associated with a before IGE episode ranged from just over twofold for FC to an approximate sixfold increase for FD.

Additional analyses were conducted to look at FGD risk after IGE with an invasive pathogen (Campylobacter, Shigella, or Salmonella infection). There were 44 infections with these pathogens reported. The overall odds for any of the FGD given an invasive IGE exposure was 4.0 ($P<0.001$), and was significant for IBS (OR 5.5, $P<0.001$) and D (OR 5.0, $P=0.02$). Constipation (OR 2.3, $P=0.10$) demonstrated a lesser effect size and FD (OR 4.0,

Table 2. Unadjusted odds ratios (95% confidence intervals) for exposure variables and other covariates from a conditional logistic regression model evaluating the risk of Functional gastrointestinal disorders among active duty US military personnel from 1999 to 2007

Variable	Constipation	Dyspepsia	Functional diarrhea	IBS
Married	1.09 (1.04, 1.13)	1.21 (1.13, 1.29)	1.45 (1.19, 1.77)	1.24 (1.19, 1.32)
<Bachelor's Degree	1.56 (1.48, 1.65)	1.17 (1.09, 1.26)	1.25 (0.99, 1.58)	1.13 (1.06, 1.20)
Non-Caucasian	1.41 (1.37, 1.46)	1.09 (1.03, 1.15)	0.68 (0.57, 0.82)	0.70 (0.66, 0.73)
Enlisted	1.75 (1.65, 1.86)	1.20 (1.11, 1.29)	1.16 (0.92, 1.47)	1.13 (1.04, 1.19)
Branch of service				
Navy	Reference	Reference	Reference	Reference
Army	1.16 (1.11, 1.21)	1.01 (0.94, 1.09)	1.34 (1.07, 1.68)	0.97 (0.92, 1.03)
Air Force	1.12 (1.06, 1.17)	1.41 (1.31, 1.52)	1.64 (1.29, 2.09)	1.50 (1.41, 1.60)
Marines	0.96 (0.90, 1.03)	0.78 (0.70, 0.87)	0.54 (0.36, 0.80)	0.79 (0.71, 0.87)
Any IGE exposure[a]				
≤6 Months	2.70 (2.41, 3.04)	3.36 (2.75, 4.11)	8.47 (5.27, 13.62)	5.19 (4.51, 5.96)
≤12 Months	2.37 (2.16, 2.60)	2.67 (2.27, 3.13)	8.99 (5.87, 13.79)	4.59 (4.10, 5.14)
≤18 Months	2.29 (2.11, 2.49)	2.53 (2.18, 2.90)	6.97 (4.81, 10.11)	4.12 (3.73, 4.57)
≤24 Months	2.18 (2.01, 2.35)	2.46 (2.15, 2.81)	5.94 (4.26, 8.28)	3.86 (3.51, 4.24)
Bacterial exposure[b]				
≤6 Months	2.53 (2.07, 3.10)	4.38 (3.13, 6.13)	15.74 (7.58, 32.69)	6.09 (4.92, 7.54)
≤12 Months	2.32 (1.99, 2.71)	3.13 (2.41, 4.05)	13.91 (7.51, 25.76)	4.98 (4.19, 5.91)
≤18 Months	2.21 (1.93, 2.53)	2.83 (2.25, 3.57)	9.63 (5.79, 15.99)	4.43 (3.80, 5.16)
≤24 Months	2.16 (1.91, 2.44)	2.68 (2.17, 3.31)	8.37 (5.30, 13.22)	4.36 (3.79, 5.01)
Viral exposure[c]				
≤6 Months	2.66 (2.31, 3.06)	2.71 (2.10, 3.50)	4.00 (2.04, 7.84)	4.49 (3.74, 5.39)
≤12 Months	2.28 (2.04, 2.56)	2.31 (1.88, 2.84)	4.45 (2.55, 7.79)	4.19 (3.63, 4.84)
≤18 Months	2.26 (2.04, 2.50)	2.16 (1.80, 2.60)	4.45 (2.70, 7.38)	3.80 (3.34, 4.33)
≤24 Months	2.14 (1.94, 2.36)	2.15 (1.82, 2.54)	4.08 (2.59, 6.44)	3.44 (3.04, 3.89)

IBS, irritable bowel syndrome; IGE, infectious gastroenteritis.
[a]Includes any IGE exposure from time indicated until censure.
[b]Includes only IGE of bacterial origin from time indicated until censure.
[c]Includes only IGE of viral origin from time indicated until censure.

$P = 0.33$) showed no significant association, though numbers were limited.

Psychological comorbidity diagnosis codes were infrequently recorded and assessment for associations between concomitant psychological diagnoses and FGD found significantly higher odds of axis II disorders in IBS (OR 1.35; 95% CI: 1.19, 1.53) cases compared with controls. Among IBS cases, no statistically significant differences in the frequency of axis I or axis II disorders were found in those with post-infectious IBS (PI-IBS; axis I: 2.14%; axis II: 15.56%) compared with those with non-PI-IBS (axis I: 1.83%; axis II: 14.22%). For FC, lower odds of axis I (OR 0.39; 95% CI: 0.29, 0.54) and axis II (OR 0.53; 95% CI: 0.47, 0.60) disorders were found in cases compared with controls, axis I (OR 0.43; 95% CI: 0.25, 0.72) disorders were found less frequently in functional D cases compared with controls, an significantly lower odds of axis II (OR 0.39; 95% CI: 0.18, 0.86) disorders in FD cases compared with controls.

DISCUSSION

In this population of predominantly young, male, healthy adults utilizing an ICD-9-CM based case definition, we estimated an overall FGD incidence of 231 (95% CI: 229, 234) cases per 100,000 p-yrs with FC having the highest incidence among the FGDs evaluated. Studies on FC incidence in comparable populations are lacking. One study looking at cumulative incidence of FC over a 12-year period (1988–2003) using a repeated survey with standard symptom-based diagnostic criteria found that among those less than age 50 years at baseline, the cummulative incidence of chronic FC was 9.2% in men and 18.3% in women (21). These estimates are higher than reported in this study, which likely underestimates true incidence as only a fraction of those who meet case definitions for FC are actually seen by a medical provider (22). A consistency in rise of FC rates, particularly among females similar to previous studies was shown (2,23). Similarly, overall IBS incidence was estimated as 66 per 100,000

Table 3. Adjusted odds ratios (95% confidence intervals) for exposure variables and other covariates from a conditional logistic regression model evaluating the risk of Functional gastrointestinal disorders among active duty U.S. military personnel from 1999 to 2007

Variable	Constipation	Dyspepsia	Functional diarrhea	IBS
Married	1.06 (1.02, 1.10)	1.17 (1.10, 1.25)	1.38 (1.12, 1.71)	1.18 (1.12, 1.24)
<Bachelor's Degree	1.48 (1.40, 1.57)	1.18 (1.09, 1.27)	1.39 (1.09, 1.78)	1.18 (1.10, 1.26)
Non-Caucasian	1.39 (1.35, 1.44)	1.13 (1.07, 1.20)	0.69 (0.56, 0.84)	0.71 (0.68, 0.75)
Branch of service[a]				
Army	1.16 (1.11, 1.22)	1.02 (0.95, 1.10)	1.45 (1.14, 1.84)	0.99 (0.93, 1.05)
Air Force	1.17 (1.12, 1.23)	1.43 (1.33, 1.54)	1.66 (1.29, 2.15)	1.44 (1.35, 1.54)
Marines	0.97 (0.91, 1.04)	0.78 (0.70, 0.88)	0.50 (0.33, 0.76)	0.75 (0.68, 0.83)
Prior exposure[b]	2.15 (1.99, 2.33)	2.39 (2.08, 2.73)	6.28 (4.41, 8.93)	3.72 (3.38, 4.11)

IBS, irritable bowel syndrome; IGE, infectious gastroenteritis.
[a]Navy service members serve as the referent category.
[b]Includes any IGE exposure within 24 months before the censure.

p-yrs (male 44, female 195) in this study population, which is quite a bit lower than two previous studies reporting incidence between 200 and 260 cases per 100,000 p-yrs (24,25). However, our rates for female are similar to that of a similar age strata from Olmsted County (24). Other reasons for lower FGD rates could be because of a "healthy" population effect of active duty military personnel, a predominantly young male population, as well as potential differences in health-care seeking behavior of individuals in the military compared with civilian populations.

We found that the odds of exposure to an antecedent IGE exposure were higher in all categories of FGD cases compared with well-matched controls. In a multivariate model, FD, and IBS were more strongly associated (OR 6.28 and 3.72, respectively), though associations were also found with FC (2.15) and D (2.39). All FGDs, with the exception of FC, had relatively higher odds of IGE exposure classified as bacterial compared with viral. Although IBS, D, and even FD have been previously associated with IGE, PI FC is less widely reported. The lower effect estimate and lack of a strong dose response effect with proximity of this outcome and exposure suggest that this association may be marginal or could alternatively be explained by somatization, which predicts presentation with both FC and gastroenteritis. Prospective studies are needed to further explore this potential link between IGE and FC.

IBS has been the 'protoype' PI FGD studied to evaluate pathophysiology and mechanism of disease (26–36). However accumulating evidence of other FGDs linked to acute enteric infections requires additional basic epidemiological research, as well as pathoetiologic studies that explore different potential mechanisms of disease (35,37–43). In our study, we found that "bacterial" exposures had stronger associations with FGDs compared with "viral" exposures, with the exception of FC that showed no obvious difference, though it is difficult to generalize about the pathoetiology from this observation because of the inherent limitations in exposure classification in this study. We were able to characterize the association between FGDs and exposures with invasive pathogens (Campylobacter, Salmonella, Shigella), wherein development of incident IBS (OR 5.5, 95% CI: 2.2–13.7) and D (OR 5.0, 95% CI: 1.3–18.6) were found, the latter of which is concordant with a reported study of Salmonella gastroenteritis and D by Mearin *et al.* (7) Additional studies are needed to link particular infections with FGDs to not only further elucidate our understanding of the pathophysiologic relationship between IGE and FGDs, but to also provide attributable burden information so that potential control mechanisms can be valued and considered.

Beyond the association with IGE exposures, other covariates were notably associated with differential risk of FGDs. Although comparable studies are lacking, we found lower education associated with increased risk of IBS, wherein other studies have found no effect (44,45), consistent results in studies looking at chronic diarrhea and D (46–49), and discordant results with one study finding lower education associated with a decreased risk of FC symptoms (49). We found an association between higher risk of IBS and non-white race, which has been inconsistently identified in previous studies (50–52), and similar findings of a prior study looking at association between race and FC (53). Our assessment of the role of psychological comorbidity in risk for FGD in this population was limited because of the fact that we could only compare concomitant axis I and II disorders at time of first visit for an incident FGD case and at time of censure for controls. We found a significantly higher rate of axis II diagnosis among IBS cases compared with controls which has been reported previously (54), though no difference in rates of psychological diagnosis between IBS cases and PI-IBS cases. For all other FGD, we found that there were lower rates of axis I and II diagnosis among cases compared with controls. The relevance and interpretation of these findings are uncertain given the limitation of this study design and assessment of true psychological comorbidity status among both cases and controls. However, it would suggest that there is significant under reporting of psychological codiagnosis in these databases, which may be because of the stigma and career implications of receiving these diagnosis among active duty military members. Future studies are warrant to more comprehensively explore the impact of both acute psychological stress (during deployment), chronic mental health conditions, and their affect on risk of and health seeking behavior for PI-FGD in this population.

Unique to this military population-based study, we were able to evaluate branch of service and risk of FGD. Compared with those in the Navy, Army, and Air Force personnel had higher overall risk of FGDs, whereas Marines had less overall risk. Possible explanations could be related to differences in health-care seeking behavior. No studies of health-care seeking behavior for FGDs in the military have been published, however a study looking at perceived need for dental care among recruits found that Navy recruits were less likely to perceive a need for dental care compared with their Army counterparts, even when controlling for dental health measures (55). Army personnel have also been reported to be more likely to join veteran health registries compared with the other services, which may be a surrogate for increased health-care seeking behavior within this service branch (56). Additional explanations could be related to service-specific exposure, differences in stress events, or psychosocial backgrounds.

There were clear limitations to this study that may have biased the estimates and limit the generalizability of these results. Use of administrative medical encounter data, specifically ICD-9 codes, and the subjective nature of FGIDs make things particularly challenging. Although we were unable to do any type of validation study given the limits on access through the DoD medical encounter database, at least one published report from a Health Maintenance Organization found a 75% positive predictive value based on paper medical record review when two ICD-9 diagnoses were required (57). Furthermore, our FGID incidence estimates appear lower than comparative US populations, thus we feel, though not perfect, our case definition may have acceptable specificity for this type of epidemiological research study. Future ICD-9 validation studies should be conducted within the DoD for FGID and other disorders of interest, and the association with IGE should be confirmed before accepting these data as generalizable. Our ability to adjust for potential confounding variables known to be associated with FGDs was limited given the data sets utilized. Conducting similar epidemiologic studies of FGDs in the well-characterized Millennium Cohort population (58) would be useful to confirm and expand upon these results, specifically with regards to evaluating the interaction between stressors and gastrointestinal infections on FGD risk. Other known limitations are related to misclassification or systematic biases inherent in utilization of medical encounter databases for epidemiologic studies. Specifically, multiple studies have demonstrated inaccuracies in ICD-9 coding (59–61). Smith *et al.* (62) evaluated correlation between patient report and medical records in the Defense Medical Surveillance System system, and described increased correlation associated with longer surveillance periods. As utilized in previous publications (14,63), we required multiple medical encounters for the same diagnosis in an attempt to minimize case misclassification. With this case-control study design, wherein some of the FGD outcomes (e.g., IBS, FD, D) and primary exposure (IGE) share clinical symptomatology, there is concern of differential exposure misclassification. In fact, we evaluated a 6-month exposure exclusion period prior to initial FGD diagnosis (or control censoring) to prevent misclassification of initial FGD presentation as an episode of IGE and found a reduction in effect estimate (OR) at 12 months to decrease by 23% for all FGD (IBS 17%, D 32%, constipation 17%, and FD 22%) which could either be because of a misclassification bias or represent a real exposure effect (the latter of which is more likely given the lack of overlap between FC symptoms and IGE). Prospective studies are needed to better evaluate the temporality of IGE exposure and FGD outcome. If the duration between exposure and disease onset was short, however, we may have under represented the true association biasing the results shown here toward the null. Although this is a less than ideal scenario, we felt it more conservative to decrease the likelihood of FGD misclassification as IGE than to increase the sensitivity of exposure identification. Furthermore, the increasing risk associated with IGE and FGD with narrowing the proximity of the exposure window further supports the association between exposure and outcome. In addition, it is conceivable that persons with undiagnosed IBS, chronic diarrhea, FC, or D may be more likely to seek medical care as a result of an IGE episode. This may be because of an increase in disease severity among persons with undiagnosed FGD, or an increased susceptibility to infectious organisms in those persons because of pathophysiological changes associated with the concurrent undiagnosed FGD. This is an inherent limitation of our study that may have artificially increased the effect estimates, though the magnitude of effect for IGE and IBS in this study is less than what has been reported in previous studies. Future studies are needed to explore differences in health care seeking behavior in FGD and non-FGD patients, as well as if susceptibility to FGDs also confers increased susceptibility to IGE (and vice versa) because of some underlying mucosal barrier, microbiota, or immunological dysfunction.

This is not the first study among military populations reporting chronic gastrointestinal complaints. After the Persian Gulf War a number of veteran studies were completed and found that chronic gastrointestinal complaints were significantly higher among veterans who deployed to the Persian Gulf compared with well-matched non-deploying control populations (59,60). Given the now known rates of infectious diarrhea during this campaign, it is quite possible that the chronic gastrointestinal complaints found in Persian Gulf War veterans may have a PI etiology. Future studies are needed, specifically among deployment populations, given the high psychological stress and high-risk IGE environments which may lead to an important interaction potentiating the risk of FGD in these settings (41,64).

These data add new perspective to the Department of Defense's consideration of the impact of infectious diarrhea during deployment, one of the most common infectious diseases encountered in that setting (65–68). The acute impact of these illnesses are significant by themselves to warrant investment in vaccine development to prevent these infections (69). Economic evaluations of traveler diarrhea vaccines have demonstrated poor to favorable cost-effectiveness performance under various scenarios when considering the primary benefit of acute disease prevention (69–71). However, if future studies confirm the pathogen-specific link to FGDs, and demonstrate the ability of vaccines to prevent these, one may envision travelers' diarrhea vaccines reaching more favorable cost-effectiveness levels or even result in a considerable

positive net present value. In the nearer term, consideration of the PI-FGD risk should prompt additional research evaluating the potential utility of early, effective antimicrobial treatment or chemoprophylaxis in the mitigation of both acute illness and chronic sequelae, as well as inform policy makers in decision to decrease the significant burden of food-borne disease globally.

CONFLICT OF INTEREST

Guarantor of the article: Mark S. Riddle, MD, DrPH.
Specific author contributions: Chad K. Porter, Robert Gormley, David R. Tribble, and Mark S. Riddle were involved in the study concept and design. Chad K. Porter and Mark S. Riddle were involved in the analysis and interpretation of data and drafting of the paper. Brooks D. Cash was involved in providing important intellectual content. All authors were involved in critical revision of the paper.
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Disclaimer

The opinions and assertions herein should not be construed as official or representing the views of the Department of the Navy, Department of the Army, the Department of Defense, or the US Government. This is a US Government work. There are no restrictions on its use.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Several studies have linked acute enteric infections with post-infectious irritable bowel syndrome.
- ✓ Limited numbers of studies have evaluated persistence of symptoms following acute diagnosis of post-infectious functional disorders.
- ✓ Chronic constipation appears to be increasing in the United States.

WHAT IS NEW HERE

- ✓ In additional to IBS (irritable bowel syndrome), other functional disorders were noted to be associated with antecedent acute gastroenteritis.
- ✓ Similar to other studies, we found a secular trend of increased rates of constipation diagnosis, particularly among active duty women in the US military.
- ✓ Infection with invasive pathogens appears to result in stronger association with post-infectious IBS compared with non-specific acute gastroenteritis.
- ✓ Post-infection functional gastrointestinal disorders appear to result in persistent health care utilization for these disorders, which represents a previously unrecognized attributable burden of disease to acute enteric infections.

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